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Late

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First Inventor John R. Lau

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Response to Office Action of January 9, 2003

Examiner Kishore:

Your action of January 9, 2003 has been received, and we offer the following responses to your objections.

1. The invention was not disclosed prior to the filing date.

2. WO 88/00474 or US 4,603,044 did not anticipate claims 5, 7-28, and 32-36. These prior art references do cite liposomes with Cr, Co, Fe or Zn complexed with iminodiacetic acid, however, the current application is different in that the instant product of the application has a large molecular weight of 1948 and is designated as a polynuclear complex. This complex is shown diagrammatically in Figure #4a and has the property of water-insolubility. It is a polymeric compound consisting of central repeating units represented by an octahedral structure and the structures are connected together by hydroxyl bridging groups. Neither Bosworth, Baldeschwieler, nor Geho describe a high molecular weight water-insoluble structure that has any similarity to the polynuclear complex. Instead they employ water-soluble chelates of small molecular weight compounds.

3. Bosworth does not anticipate claims 5, 13, 22, 24, 32-33 and 35. Bosworth does not teach how to create a polynuclear water-insoluble complex that precipitates and /or

crystallizes from aqueous media. Bosworth makes no reference to the formation of an organic-based polynuclear complex that is water-insoluble and polymerizes from an aqueous phase media over the low pH range of 3.2 to 3.3. In addition, the aforementioned paten makes no reference to the properties of the polynuclear material. These properties include the fact that the material is organic in nature, water-insoluble, possesses a dark green color, exhibits a crystal-like appearance, is a crystal-like compound exhibiting an orthorhombic structure and is 0.1 mm to 0.3 mm in length, and is soluble in organic solvents, such as chloroform: methanol (2:1 v/v) and acetonitrile.

The polynuclear complex of this application, when incorporated into the bipolar lipid membrane of a liposome is capable of targeting the liposome to the hepatocytes (metabolic cells) of the liver of a warm-blooded host. Bosworth delivers liposomes to their natural collection site, which are the Kupffer cells (macrophages) of the liver and not the hepatocytes of the liver. Kupffer cells scavenging liposomes that lack a molecular targeting means.

By contrast, this application is concerned only with the specific hepatocyte delivery of liposomes. This aspect of the application has relevance to the fact that a large variety of therapeutic and diagnostic agents need to be delivered specifically to the hepatocytes, such as insulin and serotonin.

4. Claims 5, 13, 15, 18, 22, 24, and 32-35 are not anticipated by Baldeschwieler (4,310,506). Baldeschwieler teaches the liposomal delivery of diagnostic chelates containing metals such as Cr, In, Co, and Zn with iminodiacetic acid. His liposomes also contain the usual phospholipids. However, Baldeschwieler does not teach a liposome with an insoluble polynuclear complex that the chemical property of being a hepatocyte-targeting molecule that fits into the liposome membrane. On the contrary, Baldeschwieler teaches the liposomal delivery of water-soluble chelates that are carried in the liposome's aqueous core.

In conclusion, the polynuclear complex taught in this application enables a commercially feasible product, which effectively delivers necessary and beneficial pharmaceutical and diagnostic products to the hepatocytes of liver for the treatment of significant diseases. This polynuclear complex is a specific chemical material, never before described or made, which possesses unique properties of having specificity for hepatobiliary receptors, being water-insoluble so that it incorporates into liposome membranes, and it enables a single-step liposome manufacture that is free of unwanted cross-linking that results in undesirable liposome aggregation that occurs with the sequential assembly of hepatocyte targeting systems described in the prior art.